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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/702,232	11/06/2003	Richard M. Eglen	3817.06-3	7947

23308 7590 10/04/2005

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EXAMINER	
MARVICH, MARIA	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 10/04/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/702,232	EGLEN, RICHARD M.	
	Examiner	Art Unit	
	Maria B. Marvich, PhD	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *4/7/05, 7/14/05*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11/6/03* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to an amendment filed 4/7/05 and 7/14/05. Claims 1 and 8 have been amended. Claims 1-22 are pending in the application.

Response to Amendment

Any rejection of record in the previous action not addressed in this office action is withdrawn. There are no new grounds of rejection herein and therefore, this action is final.

Priority

This application repeats a substantial portion of prior Application No. 10/292,747, filed 8/27/02, and adds and claims additional disclosure not presented in the prior application. Since this application names an inventor or inventors named in the prior application, it may constitute a continuation-in-part of the prior application. Should applicant desire to obtain the benefit of the filing date of the prior application, attention is directed to 35 U.S.C. 120 and 37 CFR 1.78.

Specifically US application 10/229,747, as well as provisional applications 60/316,248 and 60/353,086, lacks disclosure of a method drawn to analyzing the effect of inhibition of expression by an expression inhibiting nucleic acid. US application 10/229,747 is drawn to a method of assaying the status of a cell by use of alpha-complementation. While 10/229,747 contemplates the use of antisense DNA or RNAi, the purpose of these molecules is to generate cells lines in which endogenous genes are removed (see e.g. paragraph 0066). However, US 10/229,747 does not contemplate use of these molecules to target the fusion peptide comprising ED. These teachings have been added to the instant specification at the following places:

bridging paragraphs page 2-3, paragraph 0037 and the instant claims. Therefore, the priority date of the instant claims is its filing date, 11/6/03.

Response to Argument

Applicants traverse the denial of priority of the instant claims on pages 8-10 of the amendment filed 4/7/05. Applicants' clarify that the priority date of the application is not at question rather at question is whether the instant claims are supported by the parent applications. To this end, applicants argue that support for the instant claims is found in US provisional application 60/316,428 on page 8 and on page 12 of US 10/229,747. It is applicants' belief that the examiner has made an erroneous distinction between inhibitory RNA that is specific for the fusion gene and inhibitory RNA that affects the expression of the fusion gene. Referenced pages of the above applications teach use of antisense DNA or dsRNA to modify cell lines by knocking out specific genes to enhance or diminish expression of a protein. Furthermore, applicants point to page 26 of prior application 10/229,747, which teaches that cells derived from these animals express fusion protein but not natural protein.

Applicants' arguments filed 4/7/05 have been fully considered but they are not persuasive. The instant application and prior applications US 60/316,428 and US 10/229,747 discuss use of expression inhibiting nucleic acids. However, the scope of use of the instant application is distinct from that of the prior applications. Specifically, the instant application is drawn use of the expression inhibiting nucleic acid to analyze the effect on the expression of the fusion protein. Prior applications 60/316,428 and 10/229,747 teach methods of use of an expression inhibiting nucleic acid to generate knock out animals, a use not contemplated by the

instantly recited claims. Prior applications neither teach the scope of the instant application explicitly or inherently. This interpretation is not due to a misinterpretation of the use of the expression inhibiting nucleic acid to analyze expression. Rather, the lack of support of the prior applications is because use of expression inhibiting nucleic acid to analyze the effect of a fusion protein is not contemplated by US 60/316,428 whether the expression inhibiting nucleic acids are specific for the fusion protein or to inhibit expression of the fusion protein. And, such a fusion protein used in the instant application would not be found in a mammal and is specifically designed to assay effects of the expression inhibiting nucleic acid of a cell that cannot be correlated with the mammals of US 60/316,428 and 10/229,747. The use of expression inhibiting nucleic acids to generate knock out animals is well known in the art and does not provide a contribution over the prior art. This method does not provide requisite teachings for use of the expression inhibiting nucleic acids to then analyze effects on expression of fusion proteins. The passage on page 26 of US 10/229,747 actually teaches away from use of antisense RNA to inhibit expression of the fusion protein. "where antisense RNA is added to the hose cell that inhibits the natural protein but not the fusion protein". Therefore, it is concluded that prior applications 60/316,428 and 10/229,747 did not contemplate use of expression inhibiting nucleic acids to analyze the effects of expression inhibiting nucleic acids on expression of a fusion protein by contemplation of generating knock-out animals.

Claim Objections

Claim1 is objected to because of the following informalities: the claim recites "for analyzing in a cell for the effect" which is grammatically incorrect. It would be remedial to

recite "for analyzing n a cell the effect". Appropriate correction is required. **This is a new objection necessitated by applicants' amendment.**

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **These rejections are maintained for reasons of record in the office action mailed 1/24/05 and restated below.**

Claims 1 and 8 are vague and indefinite in that the metes and bounds of "affects the activity of β-galactosidase" are unclear. As the preamble states that the nucleic acid interacts with mRNA, it is unclear how the nucleic acid affects the activity of the β-galactosidase resulting form an ED-EA complex. Claim 8 further states that the "activity of said ED in forming a functional enzyme" is effected. Therefore, it appears that the inhibitor blocks formation of a functional enzyme. However, by reciting that the "activity" is effected, the actual mechanism of activity of the inhibitor is unclear.

Claim 18 is vague and indefinite in that the metes and bounds of "a gene" in line 13 are unclear. It is unclear how a "gene" can express the inhibiting dsRNA as the dsRNA is said to be RNAi which is a short sequence of RNA that can be a portion of a gene.

Claim 18 recites the limitation "said first protein fusion protein" in claim 18. There is insufficient antecedent basis for this limitation in the claim.

Claim 18 is vague and indefinite in that the metes and bounds of "ED capable of complementing said EA" are unclear. It is unclear if a separate ED protein is provided to the cell or this is the same one recited in the step (2).

Response to Argument

Applicants traverse the claim rejections under 35 U.S.C. 112, second paragraph on pages 11-14 of the amendment filed 4/7/05. Applicants argue that the amendment to claim 1 has obviated the rejection regarding "affects the activity of β-galactosidase". As to use of the term "gene" in claim 8, applicants argue that the RNAi is processed from a gene.

Applicants' arguments filed 4/7/05 have been fully considered but they are not persuasive. Claims 1 and 8 recite that the expression inhibiting nucleic acid affects the activity of the β-galactosidase resulting from ED and EA forming a functional enzyme. This recitation implies a direct effect of the expression inhibiting nucleic acid on the functional enzyme. Rather, a reading of the specification suggests that the expression inhibiting nucleic acid has an indirect effect on the functional enzyme by either modulating expression of one of the components of the functional enzyme. This effect is not reflected in the claim language. While the RNAi is processed from a gene, use of the term gene is not limited to those sequences that code for the RNAi but rather includes regulation sequences, introns, and exons that are associated with the sequences required to encode the RNAi. While applicants have indicated that all claims have been amended to overcome the claim rejections, it appears that some claims were inadvertently overlooked. Specifically, claim 18 has been rejected as "said first protein

fusion protein" lacks antecedent basis. Furthermore, claim 18 has been rejected as "ED capable of complementing said EA" s unclear.

Claim Rejections - 35 USC § 102

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 3, 6-8, 11-16 and 22 are rejected under 35 U.S.C. 102(e) as being anticipated by Thomas et al (US 6,727,070; see entire document). **This rejection is maintained for reasons of record in the office action mailed 1/24/05 and restated below.**

Thomas et al teach use of an alpha complementation system using a specialized fusion protein and structural complementation (see e.g. abstract). As demonstrated in figure 1, a fusion protein is expressed comprising the alpha or small fragment of β-galactosidase (ED). Interaction of the alpha and omega or large fragment of β-galactosidase (EA) is detectable following addition of a substrate (see e.g. col 2, line 9-48). The target protein coding sequences were cloned into a vector comprising a promoter driving expression of ED followed by the cloning site (see e.g. col 39, line 50- col 40, line 12). The fusion protein comprising the target protein and ED is expressed from a vector comprising a promoter that can be cell-type specific, inducible or constitutive. The particular promoter depends upon the cell type used (see e.g. table 1). The cells stably express EA (see e.g. col 42, line 3-5). Cells were also provided with modulators that effect protein folding and/or solubility. The modulators include antisense or

ribozymes (see e.g. col 37, line 38-44). The fusions were inducibly expressed in the cell and to determine fluorescence, the cells were lysed and the lysate was used to determine activity such as by fluorescence (see e.g. paragraph col 38, line 29-39 and col 40, 45-64). The cells are grown in a variety of compounds such as neomycin, ampicillin or IPTG (see e.g. col 40, line 38-47). Mammalian cell lines are hosts for the method of Thomas et al (see e.g. paragraph col 22, line 24-32). The components of Thomas et al together would comprise a kit.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2, 4, 5, 9, 10 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Michnick et al (2004/0241636 A1; see entire document) in view of Thomas et al (US 6,727,070; see entire document). **This rejection is maintained for reasons of record in the office action mailed 1/24/05 and restated below.**

Applicants claim a method of analyzing the effect of an expression inhibiting nucleic acid using a cell comprising an expression construct expressing a fusion protein of ED and another polypeptide to which is provided EA. The expression inhibiting nucleic acid is a dsRNA or RNAi that can effect transcription factors.

Michnick et al teach a cell-based assay useful for mapping genes (proteins) into cellular pathways using fluorescence assays (see e.g. abstract). Cells are transfected with cDNAs encoding target proteins that are involved in signaling. The sequences are cloned into pCDNA3.1 which carries a CMV promoter for constitutive expression (see e.g. col 8, paragraph 0070-0071). The effect of compounds such as decoy DNAs, dsRNA or RNAi on signaling are assayed by targeting the signaling proteins as well as transcription factors (see e.g. figure 1, paragraph 0064 and table 1). The effects of the compounds identify dynamic modulations of proteins within pathways in living cells using high-throughput assays (see e.g. paragraph 0032). An example of high-throughput assays to analyze the effect of the inhibitory compounds is by alpha-complementation comprising the large and small subunit of β-galactosidase (see e.g. paragraph 0113). Interfering RNA for example is administered to the cell as purified RNA.

Michnick et al do not teach the actual components of the method of alpha-complementation.

The teachings of Thomas et al are as above.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the methods steps for alpha-complementation as taught by Thomas et al to detect dynamic modulations of protein within pathways using alpha-complementation as taught by Michnick et al because Michnick et al teach that it is within the ordinary skill of the art to assay the effects of RNAi using alpha-complementation and because Thomas et al teach that it is within the ordinary skill of the art to use a cell comprising a fusion of ED and the protein of interest and an expression inhibiting nucleic acid to which is provided EA to assay the effect of the expression inhibiting nucleic acid. A person of skill in the art would have been motivated to

develop the alpha-complementation assay as described by Thomas et al encompassing the means described in Michnick et al due to the ease and success provided by Thomas et al to enable successful utilization of alpha-complementation. Given the teachings of the cited art and the level of skill of the ordinary skilled artisan at the time of the applicant's invention, it must be considered that said ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Claims 18-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Michnick et al (2004/0241636 A1; see entire document) in view of Thomas et al (US 6,727,070; see entire document) further in view of Allen et al (US 2004/0198967; see entire document). **This rejection is maintained for reasons of record in the office action mailed 1/24/05 and restated below.**

Applicants claim a system comprising a vector comprising an ED sequence and a multiple cloning site into which is inserted a gene and the inhibiting dsRNA under the control of a transcriptional regulatory region and an EA and a substrate for β-galactosidase.

The teachings of Michnick et al and Thomas et al are as above except:

Neither Michnick et al or Thomas et al teach that the expression inhibiting nucleic acid is expressed using a transcriptional regulatory region.

Allen et al teach methods of tissue-specific, cell-specific and/or inducible expression of RNAi (see e.g. abstract). The invention proposes the tailoring of RNA suppression by use of promoters that are specific to the application by limitation of the promoter to cell-specific or inducible types (see e.g. paragraph 0007-0010). RNAi molecules are transfected into cells on

vectors comprising a variety of promoters including cell specific as well as CMV promoter (see e.g. table 2 and figure 6). In example 2, Allen et al demonstrate tissue specific expression of RNAi following co-transfection of RNAi and the target coding sequences each expressed using a liver specific promoter (see e.g. example 2). Furthermore, use of different promoters such as expression of the target by CMV and of the RNAi by a tissue-specific promoters demonstrated that RNAi could be used to specifically inhibit expression in the particular cell types (see paragraph 0125-0127).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to express dsRNA from a vector under control of a promoter such as one that is the same or different than the target gene as taught by Allen et al to assay the effects of RNAi using alpha-complementation as taught by Michnick et al in view of Thomas et al because Allen et al teach that it is within the ordinary skill in the art to express RNAi in a tissue-specific, cell-specific or inducible manner and because Michnick et al in view of Thomas et al teach that it is within the ordinary skill of the art to assay the effect of the expression inhibiting nucleic acid using a cell-based assay comprising a fusion protein comprising ED in the presence of EA and an expression inhibiting nucleic acid. A person of skill in the art would have been motivated to express the dsRNA under control of a promoter that allows tissue specific or cell specific or inducible regulation of the RNAi for the expected benefit of limiting expression to target cells or to particular times by use of the particular promoter (see e.g. Allen et al paragraph 0007-0010). Given the teachings of the cited art and the level of skill of the ordinary skilled artisan at the time of the applicant's invention, it must be considered that said ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Response to Argument

Applicants traverse the claim rejections under 35 U.S.C. 102 and 103 on pages 14-18 of the amendment filed 4/7/05. Applicants argue that Thomas et al use the expression inhibiting nucleic acid to analyze the effect on solubility and folding whereas the instant application analyzes the effect on expression of the protein of interest. Furthermore, applicants argue that expression of the proteins in bacterial cells is not very interesting for screening drugs and limits analysis of the results are not limited to the effect of the expression inhibiting nucleic acid on the fusion protein. Applicants argue that there is no showing that the fusion protein would be stable in a mammalian cell or provide information on the degradative instability of the target protein or the interference with a pathway that provides for expression or non-expression of a protein of interest. Finally, applicants argue that the references provided in the 103 rejection are not applicable in light of the arguments regarding the priority of the instant claims.

Applicants' arguments filed 4/7/05 have been fully considered but they are not persuasive. Absent evidence to the contrary, the method steps of Thomas et al are indistinguishable from those of the instant invention. Both Thomas et al and the instant invention teach use of a fusion protein comprising ED. The fusion protein is contacted with an expression inhibiting nucleic acid and formation of a functional β-galactosidase is assayed. While the intended use of Thomas et al differs from that of the instant invention in that the solubility and folding of a resultant protein are analyzed, the method steps used to analyze the solubility and folding also lead to an analysis of the effect on the expression of an expression inhibiting nucleic acid. That Thomas et al is not useful for drug screening or cannot be used to

analyze solubility and folding is potentially reading limitations from the specification that are not explicitly recited in the instant claims. Contrary to applicants' arguments, mammalian cells and bacterial cells are contemplated by Thomas et al (see e.g. col 3, line 25-32). That the method is not functional in mammalian cells and that the fusion protein has not been demonstrated to be stable argues that the instant invention also lacks operability given that the methods are the same. The invention of Thomas et al is not limited to the intended use. Rather exposure of the components of Thomas et al to an expression inhibiting nucleic acid would inherently lead to an analysis of the effect of the expression inhibiting nucleic acid. As demonstrated above, the priority date of the instant claims is not predated by Michnick or Allen.

Conclusion

No claims allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B. Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, David Nguyen, PhD can be reached on (571)-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maria B Marvich, PhD
Examiner
Art Unit 1633

September 29, 2005

JAMES KETTER
PRIMARY EXAMINER